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Abstract

Numerous studies over the last 35 years report an increase in upper respiratory infection (URI) symptoms in athletes during periods of heavy training and competition. Challenges athletes face such as heavy exercise and life stress influence immune function via activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous-system and the resulting immunoregulatory hormones. Both innate and acquired immunity are often reported to decrease transiently in the hours after heavy exertion, typically 15–70%: prolonged heavy training sessions in particular have been shown to decrease immune function; potentially providing an 'open window' for opportunistic infections. Whether the observed changes in immunity with acute strenuous exercise or periods of heavy training account for the increased susceptibility to URI symptoms remains contentious. Nevertheless, there is little doubt that URI symptoms hinder athletic training and competition; underpinning the need to identify the prominent risk factors and appropriate countermeasures. Recent studies have identified prominent risk factors, including: intensified training in the winter; long-haul travel; low energy availability; high levels of psychological stress and anxiety; and, depression. Given the shared pathways and effector limbs for the body's response to physical and psychological challenges, it's logical that psychological strain influences immunity and illness incidence in athletes under heavy training; indeed, stress and anxiety have recently been shown to modify the immune response to exercise. This mini-review provides new insights and evidence-based recommendations for coping with the various challenges that athletes encounter on immune health, including: heavy exercise; life stress; sleep disruption; environmental extremes and nutritional deficits.

Keywords: Exercise; Immune; Infection; Stress; Sleep; Diet; Supplement

Highlights

- It's a widely held belief that athletes experience a decrease in immunity and an increased risk of upper respiratory infection (URI) during periods of heavy training and competition.
- Recent research highlights that key risk factors for URI in athletes include: long-haul travel; low energy availability; high levels of psychological stress and anxiety; symptoms of depression and periods of intensified training during the winter.
- Athletes frequently encounter challenges to immunity including: heavy exercise; life stress; sleep disruption; environmental extremes and nutritional deficits.
- This mini-review provides evidence-based recommendations for maintaining immune health and avoiding infection in athletes.

Background and overview of stress-immune interactions

Numerous studies over the last 35 years indicate a decrease in immunity and an increase in upper respiratory infection (URI) symptoms in athletes during periods of heavy training and competition (Peters & Bateman, 1983; Tomasi et al., 1982; Walsh et al., 2011b). Experts attribute these observations to the various challenges athletes encounter during heavy training and competition e.g. heavy exercise and life stress (Figure 1). Psychological stress and physical exertion have long been known to influence the sympathetic-adrenal axis and pituitary-adrenal axis since the pioneering work of Walter B Cannon (who coined the 'fight or flight' response) and Hans Selye (who coined the term 'stress') in the 1930s. These common pathways and shared effector limbs for the body's response to stress in its many forms give rise to increases in circulating catecholamines and glucocorticoid hormones: these

hormones are widely acknowledged to alter immune function (Dhabhar, 2014) (Figure 2). The immune system is highly organised to provide a potent, multi-layered defence against attack from pathogenic micro-organisms including viruses, bacteria, fungi and protozoa; in addition, the immune system provides defence against cancer through anti-tumour activity. The various cellular and soluble elements in the immune system's armoury against infectious agents can broadly be divided into innate (non-specific) and acquired (specific) arms. On encountering a pathogen the first line of defence, the innate immune system, is activated: the innate immune system comprises physical and chemical barriers (e.g. the skin and mucosal membranes) and phagocytes (e.g. neutrophils, monocytes etc.) that ingest and kill microorganisms along with other non-specific killer cells. The second line of defence, the acquired immune system, is highly specialized, yet slower to deploy than the innate immune system: the acquired immune system comprises the lymphocytes; specifically, T and B lymphocytes that proliferate and serve a multitude of roles including B cell antibody production, cytotoxic T cell killing and the development of T memory cells so that an augmented response can be mounted on subsequent pathogen exposure (the scientific basis for Edward Jenner‘s discovery of vaccination). Although sub-dividing the immune system into innate and acquired arms affords a simple description, this distinction is rather crude: the innate and acquired immune systems are actually very much intertwined; for example, the processes of antigen presentation and recognition and pathogen exclusion require cells of the innate and acquired immune system to work together in harmony. For a more comprehensive review of the inner-workings of the immune system and the neuroendocrine responses to stress readers are directed elsewhere (Dhabhar, 2014; Gleeson et al., 2013). The aim of this mini-review is to provide new insights about and, where possible, evidence-based recommendations for coping with the various challenges that athletes encounter on immune

health; including, heavy exercise, life stress, sleep disruption, environmental extremes and nutritional deficits (Figure 1).

Heavy exercise

In athletes under heavy training both innate and acquired immunity are often observed to decrease transiently during the recovery period after prolonged heavy exertion (≥ 90 min); typically of the order 15–70% (Bruunsgaard et al., 1997; Diment et al., 2015; Nieman, 1994; Robson et al., 1999; Tomasi et al., 1982; Walsh et al., 2011b). An overview of the changes in immunity after prolonged exercise is provided in Table 1: interested readers are directed to a comprehensive review on the topic (Peake et al., 2017). Seminal work in 1982 by Tomasi and colleagues showed lower levels of saliva immunoglobulin-A (IgA) in cross-country skiers at rest compared with age-matched controls and a further reduction in saliva IgA after competition (Tomasi et al., 1982). The temporary decrease in immune function after heavy exercise was first proposed to provide an 'open window' for opportunistic infections in landmark reviews in 1988 (Fitzgerald, 1988; Keast et al., 1988). Periods of overreaching and longer term maladaptation (coined 'overtraining') in particular have been shown to decrease immunity (Verde et al., 1992; Walsh et al., 2011a). But whether the observed changes in immunity with acute heavy exercise and intensified training are sufficient to increase URI susceptibility in accordance with the 'open window' theory remains a point of contention (Martensson et al., 2014; Walsh & Oliver, 2016). As logic dictates, a high training volume, as would be required by an international endurance athlete, is incompatible with frequent URI (Martensson et al., 2014). Empirical evidence, albeit in a small number of athletes, indicates that international athletes suffer fewer not greater URI episodes than national level athletes

(Hellard et al., 2015) and that URI incidence correlates negatively with training load, *viz*. 'the less sick the more the athlete can train' (Martensson et al., 2014). However, there may be genetic and/or modifiable behavioural factors that account for why international athletes succumb to fewer URI's than national level athletes during high-volume training. For example, there may be host genetic influences on URI (Trammell & Toth, 2008); whereby, elite athletes may be predisposed to have a more efficacious immune response to challenge with respiratory viruses; but this remains speculative. Recent evidence lends some support for this notion by showing that gene polymorphisms for the high expression of pro-inflammatory cytokines predict URI in highly trained athletes (Gleeson et al., 2017). It's quite conceivable that the observation of lower URI incidence in international *vs*. national athletes (Hellard et al., 2015) can be explained more simply by improved lifestyle behaviours in international athletes that alter infection risk; for example, better hygiene, infection avoidance, diet, sleep and stress management as a result of experience and/or access to better education (Walsh & Oliver, 2016). It's also conceivable that international athletes who receive funding are less likely to have to balance a full-time job alongside their training and competition schedule and so experience less overall stress; this in-turn could account for their reduced susceptibility to URI (life stress and immune health is discussed in the next section). Notwithstanding, recent work indicates that high level athletes experience an increased susceptibility to URI symptoms during heavy training in the winter; particularly, when implementing increases in training load (Hellard et al., 2015; Svendsen et al., 2016). As such, when scheduling training programmes, wherever possible, coaches should follow these training-related recommendations adapted from the Exercise Immunology Society position statement (Walsh et al., 2011a).

Recommendations for modifying training and recovery activities to maintain immune health in athletes

1. Manipulate training volume and/or intensity to manage training load
2. Keep the size of increments in volume and intensity to 5-10% per week; particularly important during winter
3. Increase the frequency of shorter, spike training sessions rather than enduring fewer but longer sessions
4. Implement recovery activities immediately after the most intensive training sessions
5. Undertake easy-moderate training sessions after each high intensity session
6. Plan an easier recovery/adaptation week every 2nd or 3rd week of the training cycle
7. Permit athletes at heightened risk of illness several weeks of active recovery after completion of a season or major competition

Life stress and other aspects of psychological wellbeing

Psychological stress has a well-known and marked influence on immunity (see comprehensive review by Dhabhar (2014)) and infection resistance (Cohen et al., 1991). Given the shared pathways and effector limbs for the body's response to various challenges (Figure 2), it stands to reason that psychological stress plays a role in the decrease in immunity with prolonged heavy exercise and heavy training (Walsh & Oliver, 2016). Athletes may experience psychological stress associated with competition, injury, team selection, travel, sleep disruption and jetlag; in addition, they may also experience psychological stress in their personal life related to relationship difficulties, financial hardship and bereavement. Unfortunately, exercise immunologists have rarely reported, let alone taken

account of, psychological stress in their studies and so there is little by way of empirical evidence to support this contention. Supporting evidence is beginning to emerge however, as new research shows that the level of state-anxiety (tension and worry right now) and perceived stress (life stress in the last month) reported before exercise modify the *in-vivo* immune response to subsequent exercise (Edwards et al., 2018). Individuals reporting moderate state-anxiety before exercise had greater *in-vivo* immune responses after subsequent exercise of various intensities and durations than those reporting low state-anxiety before exercise. These findings accord with the immune-enhancement theory of moderate stress (Dhabhar, 2014). Perhaps the most illuminating finding in the Edwards et al. (2018) study was that the correlation between pre-exercise state-anxiety and *in-vivo* immunity after exercise (*r* 0.39) was as strong as the correlation between physiological stress during exercise and *in-vivo* immunity after exercise (heart rate training impulse: *r* - 0.37). These findings demonstrate an important moderating influence of pre-exercise psychological stress on the immune response to exercise. They also raise the prospect that accounting for psychological strain during prolonged exercise as well as before exercise might explain an even greater proportion of the variance in immunity after heavy exercise (*vs*. assessing pre-exercise psychological strain alone). Continued research efforts are needed to extend the scope of the Edwards et al. (2018) findings to understand how high levels of psychological stress (e.g. during important competition or major life events) might impact immunity and infection incidence in athletes. As might be expected, research from the field of psycho-neuro-immunology indicates that chronic high stress, impairs the immune response to challenge (Dhabhar, 2014). In terms of real-world clinical relevance, recent and timely evidence highlights that aspects of mental health including psychological stress, anxiety and depression are important risk factors that raise the incidence of illness in Olympic athletes (Drew et al., 2017).

Exercise immunologists are recommended to include aspects of mental health (e.g. psychological stress and depression) in a broader conceptual framework of exercise-immune interactions alongside other lifestyle factors (Figure 1). Due consideration should be given to the individual athlete's cognitive appraisal of the various challenges they face (i.e. coping *vs*. overloaded): it has long been known that the emotional experience evoked by different situations influences the neuro-endocrine response (Lundberg & Frankenhaeuser, 1980) (Figure 2). Adopting this broader conceptual framework will inform and direct fruitful research questions and experimental designs; in turn, improving our understanding of the complicated exercise-immune interactions. In time, this work may lead to effective countermeasures to immune impairment in high level athletes. There is good reason for optimism as a programme of mindfulness meditation increased the antibody response to influenza vaccine in employees working in a highly stressful environment (*vs*. waiting-list controls) (Davidson et al., 2003). Fruitful avenues for enquiry include determining the extent to which neuro-endocrine-immune responses to exercise are hard-wired; *viz*., some athletes may be predisposed to low immune reactivity and some to high immune reactivity. For example, it remains to be shown whether trait-anxiety and other stable personality characteristics play a role in determining the strength of immune reactivity to exercise. In line with this contention, negative personality disposition (high neuroticism, low agreeableness and openness) has been shown to blunt stress reactivity to psychological stressors (Bibbey et al., 2013). Due consideration should also be given to a possible role for stressful early life experiences in shaping immune reactivity and host defence across the lifespan (Elwenspoek et al., 2017). Exciting new findings show that adults whose parents lived apart and never spoke during their childhood were more than three times as likely to develop a common cold

when exposed to the upper respiratory virus than adults from intact families (Murphy et al., 2017).

Whenever possible, and with the help of an accredited sports psychologist, athletes should follow these practical recommendations.

Recommendations to optimise psychological wellbeing and maintain immune health in athletes

1. Keep unnecessary life stress to a minimum
2. Monitor and manage all forms of stress - psychosocial and physical
3. Monitor life demands e.g. using the DALDA questionnaire[1]
4. Monitor mood[2], stress[3] and anxiety[4]
5. Implement stress management intervention, where necessary

[1]Daily Analysis of Life Demands in Athletes (Rushall, 1990); [2]Profile of Mood State (Morgan et al., 1987); [3]Perceived Stress Scale (Cohen et al., 1983); and, [4]Stait-Trait Anxiety Inventory (Spielberger, 1983).

Sleep disruption

Like the other forms of stress discussed, sleep disturbances are considered to influence immunity (see comprehensive review by Irwin (2015)) via activation of the hypothalamic–

pituitary–adrenal axis and the sympathetic nervous-system (Figure 2) (Peake et al., 2017). Chronic sleep disturbance and disruption to the normal circadian rhythm (e.g. shift work) are associated with inflammation and desynchronization of rhythmic immune variables; likely contributing to increased risk of infection, cardiovascular disease, and cancer in long-term shift workers (Mullington et al., 2010). There is now evidence that athletes experience poor sleep patterns compared with non-athletes; for example, sleep efficiency (% time asleep) assessed using actigraphy was 81% in elite athletes compared with 89% in non-athletes (Leeder et al., 2012): sleep efficiency <85% is deemed abnormal (Cohen et al., 2009). Unfortunately, work to date only begins to scratch the surface regarding how sleep disturbance influences the immune response to exercise. When considering the potential effects of poor sleep on immunity in athletes, it is important to distinguish between acute (e.g. 1 night of disrupted sleep) and chronic sleep disturbance (e.g. many nights of disrupted sleep). Compared with normal sleep, a disrupted night's sleep appears to prime the immune system and enhance immune-surveillance by stimulating total lymphocytes, cytotoxic T cells and natural killer cells to leave the blood and migrate to potential sites of infection during the early recovery period after exercise (Ingram et al., 2015). Although missing one night of sleep may decrease endurance performance (Oliver et al., 2009), laboratory studies indicate that a night without sleep does not influence leukocyte trafficking, neutrophil degranulation, or mucosal immunity at rest or after exercise (Peake et al., 2017). Subtle immune changes have been observed after a night without sleep, including a shift from a T helper 1 cytokine profile (e.g. interferon-γ) toward a T helper 2 cytokine profile (e.g. interleukin-10) (Irwin, 2015). This might be detrimental to host defence during longer-term sleep disturbance as T helper 1 cytokines such as interferon-γ provide important protection against intracellular viral and bacterial challenge. Chronic sleep disturbance (≥10 nights, 50% sleep loss) increases the plasma inflammation markers C-reactive protein and IL-6 (Haack et al., 2007; Peake et al.,

2017). However, intervening daytime naps can counter this apparent inflammatory response (Shearer et al., 2001).

It is uncertain whether subtle immune modifications with acute sleep loss in athletes are clinically meaningful; moreover, unlike military personnel, athletes rarely intentionally miss a whole night's sleep (Peake et al., 2017). Nevertheless, landmark studies by Dr Sheldon Cohen's team demonstrate the real-world clinical importance of longer-term, good sleep habits for immunity. In one such study, short sleep duration (< 7 h/night) in the 7 days surrounding hepatitis B vaccination decreased the anti-hepatitis-B antibody response and the likelihood of clinical protection (Prather et al., 2012). In other studies, those sleeping < 6 h per night and those with sleep efficiency < 92% the chance of developing a common-cold after intra-nasal inoculation with rhinovirus increased ~4-5 times (Cohen et al., 2009; Prather et al., 2015). Besides the obvious strength of using a live common cold challenge, these two studies also controlled for psychological factors (e.g. perceived stress). Psychological stress could conceivably account, at least in part, for the influence of sleep disruption on immunity in many papers. In keeping with a conceptual framework that incorporates the athlete's cognitive appraisal of the situation (Figure 2), one might anticipate different immune responses in the controlled laboratory environment, where participants are fully prepared for a night or more of sleep disruption, than a real-world scenario where sleep disruption may be unanticipated and particularly unpleasant (e.g. related to long-haul travel, life stress etc.).

Continued research efforts should be directed towards monitoring and improving sleep hygiene in athletes, and to improving our understanding of the implications for immunity of

various sleep behaviours adopted by athletes e.g. sleep restriction or sleep extension. For example, recent findings show that individuals develop resilience to the subjective fatiguing effects of restricting sleep in the working week (4 h/night) and 'catching-up' at the weekend (8 h/night) (Simpson et al., 2016). However, the authors contend that this apparent resilience to sleep restriction may come at a cost to long-term health: after only 3 weeks, they observed activation of physiological stress systems and altered interplay with inflammation; including, dysregulated cortisol 24 h rhythm and increased cortisol sensitivity in monocytes. In direct contrast, sleep extension, rather than restriction, has been in the spotlight recently as a possible method to improve athlete performance. Preliminary laboratory work shows increased muscular performance with ~2 hours additional sleep each night (Arnal et al., 2016). The influence of sleep extension on immune health in high level athletes certainly warrants investigation. As does the purported benefit of going 'screen-free' during the bedtime routine to increase sleepiness and improve sleep quality (Gronli et al., 2016); likely due to reducing blue-enriched light known to block the soporific hormone, melatonin. Whenever possible, athletes should follow these practical sleep recommendations.

Sleep recommendations to maintain immune health in athletes

1. Aim for > 7 h sleep each night
2. Avoid restricting sleep over many days and 'catching-up'
3. Monitor morning freshness and vigour
4. Consider monitoring sleep duration and efficiency using a wearable device
5. Daytime naps may be beneficial

6. Optimize sleep hygiene routine in the hour before bedtime e.g. reduce psychological strain and go ‘screen-free’
7. Ensure darkness at bedtime

Environmental extremes

The body’s response to the challenge of heat or hypoxia is initiated and coordinated by the central nervous system with the effector limbs, the hypothalamic–pituitary–adrenal axis and the sympathetic nervous-system, producing the immunoregulatory hormones (Figure 2: comprehensively reviewed in Gleeson et al. (2013)). Dr Roy Shephard hypothesized that exercise in adverse environments, with stereotyped stress hormone responses over and above those seen during exercise in favourable conditions, may cause greater disruption to immune function and host defence (Shephard, 1998). During regular training and competition, many athletes experience exertional hyperthermia (core temperature > 39.5°C), dehydration, peripheral cooling and moderate altitude or hypoxia (up to ~2500 m). A few athletes also experience more extreme thermal stress such as exertional heat illness casualties (core temperatures can be > 41°C) and hypothermic casualties (core temperature < 35°C, e.g. open water swimmers) and high altitude (up to 5000 m) is experienced in athletes participating in adventure races or intermittent hypoxic training (Walsh & Oliver, 2016).

Laboratory studies where core temperature remains within 2°C of normal baseline indicate a rather limited effect of either hot or cold environments on immune function; the only possible exception is T-cell mediated immunity that has been reported to decrease when heat is

superimposed onto exercise (Severs et al., 1996). As such, most of the available evidence from laboratory studies does not support the contention that exercising in the heat or cold poses a greater threat to immune function compared with thermoneutral conditions (Walsh et al., 2011a). It is worth noting that individuals exercising in environmental extremes (e.g. hot *vs.* temperate or hypoxia *vs*. normoxia) tend to fatigue sooner or reduce their work rate so their exposure to exercise stress in the heat (or hypoxia) tends to be self-limiting.

A popular belief held by many athletes is that breathing cold, dry air and getting a 'chill' through cooling of the skin cause the 'common cold'. Although controversial, some evidence shows that peripheral cooling of the nose and upper airways (and even the feet) can increase URI symptoms; indeed, peripheral cooling may inhibit immune cell trafficking and create a suitable local environment for viral replication (Johnson & Eccles, 2005). In support of this contention, recent research provides the missing piece of the jig-saw by showing that the human rhinovirus, a common cold causing virus, replicates more robustly at cooler temperatures found in the nasal cavity (33-35 °C) (Foxman et al., 2016). The temperature-dependent rhinovirus amplification is largely a result of host cell antiviral restriction mechanisms operating more effectively at 37 °C than at 33 °C (Foxman et al., 2016). This research may at last provide an explanation for why cold ambient conditions often precede outbreaks of URIs such as the common cold (Makinen et al., 2009). With this in mind, wherever possible, athletes are recommended to take extra precautions to avoid breathing large volumes of cold, dry air when training and competing in the winter.

Altitude training typically involves athletes being exposed passively or whilst exercising in hypoxia for 1−6 hours per day for 5−14 days. Whilst there is continued debate over the benefits to sport performance, there is relatively little discussion and research about how various altitude-training methods affect immunity and host defence in athletes (Walsh & Oliver, 2016). This is concerning as the consensus is that altitude and hypoxic exposure decrease both *in-vivo* and *in-vitro* cell-mediated immune function and increase URI symptoms (Oliver et al., 2013; Pyne et al., 2000). Nevertheless, caution is required when interpreting findings from studies of self-reported URI at altitude as there is considerable overlap between URI symptoms and acute mountain sickness. One emerging trend from the literature is that immunity and host defence are typically decreased in studies where athletes complete live-high train-high or live-high train-low altitude training methods but not in studies involving intermittent hypoxic training (Walsh & Oliver, 2016).

Athletes are also exposed to environmental stress outside of training. For example, during long-haul air travel, which is common for elite athletes (Figure 1), hypobaric-hypoxia in the aircraft cabin exposes athletes to altitudes equivalent to 1800−2400 m (Wilder-Smith et al., 2012). This coincides with studies reporting a two-to-five-fold increase in URI symptoms with long-haul travel (Schwellnus et al., 2012; Svendsen et al., 2016). Studies are required to determine whether the increase in URI symptoms with long-haul travel is due to hypoxia-induced immune alterations, increased exposure to pathogens in the aircraft cabin, or some other mechanism. It's quite conceivable that the increase in psychological stress, anxiety and travel fatigue associated with long-haul travel to training camps and competitions may increase URI. For example, athletes may experience anxiety related to fear of flying, flight

delays and baggage issues; they may also experience travel fatigue related to sleep loss and jet lag.

Research is required to improve our understanding of the influence of increasingly common post-exercise/recovery practices that involve environmental extremes on immune health. For example, cryotherapy by cold-water immersion or cold-air exposure and heat acclimation by post-exercise hot bath are becoming increasingly popular (Tipton et al., 2017; Zurawlew et al., 2016). Research suggests that immune health may actually be enhanced by regular, intermittent exposures to environmental stress e.g. intermittent hypoxia or cold water immersion (Walsh & Oliver, 2016). Exciting recent work shows that taking a (hot-to-) cold shower for 30 s each day decreases sickness absence from work by almost 30% (Buijze et al., 2016). Clearly, the potential for immune-enhancing effects of post-exercise cold or hot exposure is a fruitful avenue for enquiry. Whenever possible, athletes should follow these practical recommendations to maintain immune health in environmental extremes.

Recommendations to maintain immune health in athletes encountering extreme environments

1. Carefully manage training load and recovery when training with additional heat and/or hypoxia
2. Acclimation to heat and/or hypoxia may limit the influence of environmental extremes on immune health
3. Take extra precautions to avoid prolonged periods breathing large volumes of cold, dry air e.g. when training and competing in the winter

4. Personal hygiene, sleep hygiene, proper nutrition and reducing unnecessary stress become increasingly important during long-haul travel to training camps and competition
5. Short-lasting exposure to environmental extremes may enhance immunity and reduce sickness e.g. 30s (hot-to)-cold showers

Nutritional deficits and the value of supplements

For an extensive review on this subject readers are directed to a recent position stand (Bermon et al., 2017). Whenever possible, athletes are recommended to ensure their diet meets their energy demands and provides sufficient macro- and micro-nutrients to support their immune system (Gleeson et al., 2013). Nutrient availability can influence immunity directly because macro- and micro-nutrients are involved in a multitude of immune processes (e.g. as a fuel source) but also indirectly via increases in immunosuppressive stress hormones during prolonged exercise (Figure 2). For example, when blood glucose falls during prolonged exercise the glucocorticoid cortisol increases; providing the rationale for many studies investigating carbohydrate ingestion during prolonged exercise as a countermeasure to immune impairment (Henson et al., 1998; Walsh et al., 2011a). Despite much interest and fervour amongst exercise immunologists, promising early findings demonstrating the benefits of carbohydrate sports drinks to blunt *in-vitro* immune impairment with heavy exercise have not been realised in studies assessing clinically relevant *in-vivo* immunity (Davison et al., 2016) and URI in marathoners (Nieman et al., 2002). The same criticism can be levelled at many supplements claimed to bolster or boost athlete immunity: studies have failed to show consistent and clinically meaningful positive effects of nutritional supplements on athlete

immune health (Bermon et al., 2017). Support for nutritional supplements to enhance immunity largely comes from studies in those with compromised immunity, such as the elderly and clinical patients; not, from young, otherwise healthy individuals who might have little to gain from such supplements. Accepting this viewpoint ignores the recommendation about matching energy intake to expenditure and providing sufficient macro- and micro-nutrients to maintain immunity. Indeed, there are various real-world athlete scenarios where energy, macro- and micro- nutrient intake may be insufficient (Table 2). In the real-world, athletes may intentionally experience deficits in energy intake (e.g. weight-loss diets) and macronutrient intake (e.g. train-low- or sleep-low-carbohydrate). Short-term energy restriction over a few days can compromise immunity (Bermon et al., 2017; Walrand et al., 2001) and long-term low energy availability has recently been associated with illness in Olympic athletes (Drew et al., 2017). There may also be other times when athletes experience a down-turn in host defence and/or increased exposure to pathogens, e.g. foreign travel for training camps and competitions (Svendsen et al., 2016) and when training and competing during the wintertime (Hellard et al., 2015). As such, there are specific scenarios when athletes might benefit from nutritional supplements to support immunity (Table 2) (Bermon et al., 2017).

Paradoxically, nutritional strategies currently adopted by endurance athletes, including training-low- and sleeping-low-carbohydrate (Marquet et al., 2016), may benefit training adaptations and performance at the expense of immunity (Table 2); for example, carbohydrate restriction may increase the immunosuppressive stress hormone response to exercise (Bermon et al., 2017). As such, any benefits laboratory studies show in terms of training adaptations and performance might, in the long term, be lost if the athlete gets sick and is not available to train. Studies are required to investigate whether the nutritional

practices adopted by elite athletes impair immunity and increase infection; and, whether nutritional supplements benefit immune health in the scenarios outlined in Table 2 without blunting training adaptations and without side effects. Where possible, a distinction should be made between supplements that bolster (i.e. restore) immunity in athletes with underlying inadequacies and those purported to boost immunity in athletes with no underlying inadequacies. Recent Cochrane reviews have noted the low quality of many studies on nutritional supplements to support immune health; specifically, small samples, poor controls and unclear procedures for randomisation and blinding were commonplace (Hao et al., 2015). Clearly, there is a pressing need for randomized controlled trials in high level athletes with sufficient participant numbers; rigorous controls and procedures; appropriate supplementation regimens; and, clinically meaningful measures of immunity. Whenever possible, athletes should follow these simple nutritional recommendations to maintain immune health.

Nutritional recommendations to maintain immune health in athletes

1. Match energy intake to expenditure
2. Avoid crash dieting
3. Eat a well-balanced diet
4. Consume >50% daily energy intake as carbohydrate
5. Ensure adequate protein intake (1.2−1.6 g/kg body mass/day)
6. Consider 1,000 IU/day vitamin D_3 from autumn to spring to maintain sufficiency
7. At the onset of a cold take zinc acetate lozenges (75 mg/day)
8. Consider probiotics ($\geq 10^{10}$ live bacteria/day) for illness prone/travelling athlete

10 recommendations to avoid infection and maintain immune health in athletes

Finally, incorporating the key recommendations from the other sections in this mini-review, these 10 practical recommendations to avoid infection and maintain immune health should be followed by all athletes. Practising good hand hygiene, avoiding self-inoculation by touching the eyes, nose and mouth, following a proper vaccination schedule and avoiding training and competing with *'below-the-neck'* (systemic) symptoms represent simple, sound advice to avoid infection (Van Tonder et al., 2016; Walsh et al., 2011a).

1. Try to avoid sick people, particularly in the autumn-winter
2. Ensure good hand hygiene[1] and appropriate vaccination[2]
3. Avoid self-inoculation by touching the eyes, nose and mouth
4. Do not train or compete with *'below-the-neck'* symptoms
5. Monitor and manage all forms of stress including physical and psychosocial
6. Carefully manage increments in training stress
7. Replace overly-long training sessions with more frequent spike sessions
8. Plan recovery or adaptation week every 2nd or 3rd week
9. Aim for at least 7 h sleep each night
10. Eat a well-balanced diet and avoid chronic low energy availability

[1]Hand hygiene advice at www.cdc.gov/handwashing. [2]Appropriate vaccination schedule should be discussed with the general practitioner; resources include www.nhs.uk/conditions/vaccinations and www.cdc.gov/vaccines.

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Table 1. Overview of the typically transient (lasting < 24 h) changes in immunity after prolonged heavy exercise.

Immune aspect	**Influence of prolonged heavy exercise (≥ 90 min)**
Innate immunity ('front-line' defence)	*Counts* ↑ Neutrophils, 'neutrophilia' peaks 2-3 h post ↑ Immature neutrophils in circulation ↑ Monocyte counts, 'monocytosis' peaks 1-2 h post ↑ Proinflammatory monocytes (CD14+/CD16+) *Functional aspects* ↓ Neutrophil respiratory burst (mitogen-stimulated) ↓ Neutrophil degranulation (bacterial-stimulated) ↓ NK cell activity ↓ Monocyte toll-like receptor (TLR1-4) expression ↓ Macrophage antigen presentation capacity (in mice) ↓ Monocyte cytokine secretion (LPS-stimulated) ↓ Macrophage resistance to HSV-1 infection (in mice)
Mucosal immunity ('front-line' defence)	↓ Saliva SIgA concentration or secretion rate ↓ Tear fluid SIgA concentration ↑ Saliva lysozyme, lactoferrin and α-defensin secretion rate ↑ α-amylase activity
Acquired immunity ('second-line' defence)	*Counts* ↑ Lymphocytes (↑ T, B and NK cells), immediate 'lymphocytosis' ↓ Lymphocytes, 'lymphopenia' 0.5 h post ↓ T-helper CD4+/T-suppressor CD8+ ratio ↑ Effector/cytotoxic lymphocyte egress to tissues (NK, γδT and CD8+ T cells) *Functional aspects* ↓ *In-vivo* response to novel challenge e.g. DTH, CHS skin tests ↓ *In-vivo* response to previously encountered challenge ↓ T cell proliferation (mitogen-stimulated) ↓ % T cells producing effector cytokines (mitogen-stimulated) ↓ T cell homing/migration (towards Rhinovirus) - Serum immunoglobulin unchanged (IgA, IgG and IgM)

NK = natural killer; LPS = lipopolysaccharide; HSV-1 = herpes simplex virus type 1; SIgA = secretory immunoglobulin-A; γδT = gamma delta T cells; DTH = delayed type hypersensitivity; CHS = contact hypersensitivity.

Table 2. Value of nutritional supplements for reducing common cold and maintaining immunity in various athlete scenarios. Adapted from Bermon et al. (2017).

Scenario	**Immune health and performance**	**Supplement**	**Supporting evidence and knowledge gaps**
Winter season	Common cold and Influenza season; URS decrease training and performance; low UVB skin exposure decreases vitamin D	Vitamin D_3	Moderate support for vitamin D in athletes/military; recommend monitoring vitamin D and in those insufficient (25(OH)D <50 nmol/L) consider 1,000 IU/day D_3 from autumn to spring to achieve and maintain sufficiency (He et al., 2016)
		Vitamin C	Moderate support in athletes/military; Cochrane review of 5 studies in heavy exercisers (n=598) shows ~50% decrease in URS taking vitamin C (0.25–1.0 g/day); unclear if antioxidants blunt adaptation in well-trained; further support required (Hemila & Chalker, 2013)
		Probiotics	Moderate support in athletes with daily dose of ~10^{10} live bacteria; Cochrane review of 12 studies (n=3720) shows ~50% decrease in URS incidence and ~2 d shortening of URS; minor side effects (Hao et al., 2015)
		Glutamine	Limited support; glutamine (2 x 5 g) decreased URS after endurance races; this dose does not maintain blood glutamine or alter immunity; mechanism for therapeutic effect unclear; further studies required (Bermon et al., 2017)
Suffering URI	URS decrease training and performance; particularly in illness prone	Zinc lozenges	Moderate support; Cochrane review shows benefit of zinc acetate lozenges (75 mg) to decrease duration of URS; must be taken < 24 h after onset of URS; side effects include bad taste and nausea (Singh & Das, 2013)

		Vitamin C	No support; Cochrane review show no benefit of 'initiating' vitamin C supplementation (> 200 mg/day) after onset of URS (Hemila & Chalker, 2013)
Foreign travel	Increased URS risk; stress prior to travel may decrease immunity; increased exposure to pathogens; Travellers' Diarrhoea and risk of dehydration	Probiotics	Moderate support; probiotics can reduce risk of Travellers' Diarrhoea; probiotics do not decrease episode duration; minor side effects; further studies required (Lomax & Calder, 2009)
Energy deficit	Training with energy deficit decreases performance and immunity	Multi-vitamin/ mineral; probiotics; bovine colostrum etc.	Limited support for supplements to reduce URS and bolster immunity in these scenarios; unclear if multivitamin/mineral supplement provides insurance; unclear if antioxidants blunt adaptation in well-trained; impact of train-low, sleep-low CHO on immune health remains unclear; further studies required (Bermon et al., 2017)
Train-low, sleep-low CHO	CHO restriction/periodization may increase adaptation and performance but decrease immunity		
Training camp	Threats to immunity include: increase in physical exertion; other stressors e.g. psychological, altered sleep, heat and/or altitude; limited food choices; energy deficit		

URS = upper respiratory symptoms; URI = upper respiratory infection; CHO = carbohydrate.

Figure Legends

Figure 1. Key factors that can lower immunity in the athlete.

Figure 2. Common pathways for the immune response to physical and psychological challenges. Physical and psychological challenges are characteristically met by a series of coordinated hormonal responses controlled by the central nervous system. Cognitive appraisal of the situation and the individual's perceived ability to cope are important in determining whether the challenge is deemed as pleasant or adverse (i.e. stressful); in turn, this influences the neuro-endocrine-immune modulation. The central control station resides within the hypothalamus, with the hypothalamic-pituitary-adrenal (HPA) axis and sympatheticoadrenal-medullary (SAM) axis providing the effector limbs by which the brain influences the body's response to challenge by controlling the production of adrenal hormones known to modulate immune function. The HPA axis regulates the production of the glucocorticoid, cortisol by the adrenal cortex and the SAM axis regulates the production of catecholamines (epinephrine and norepinephrine) by the adrenal medulla. Aside from these dominant axes, anterior pituitary hormones with known immune-regulatory effects, such as growth hormone (GH) and prolactin, may also be released in response to challenge. Sympathetic nerve innervation of organs of the immune system (e.g. primary lymphoid tissue) also indicates an autonomic nervous system involvement in the immune response to challenge.

Figure 1.

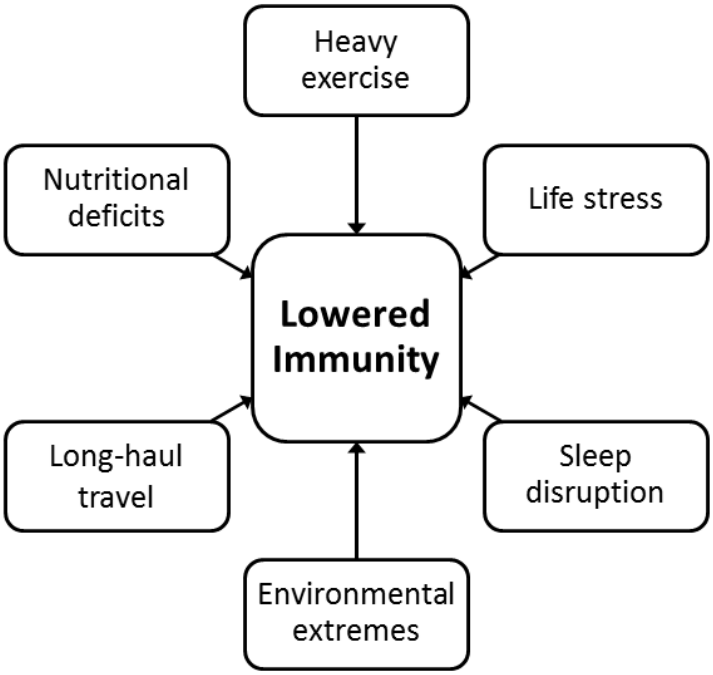
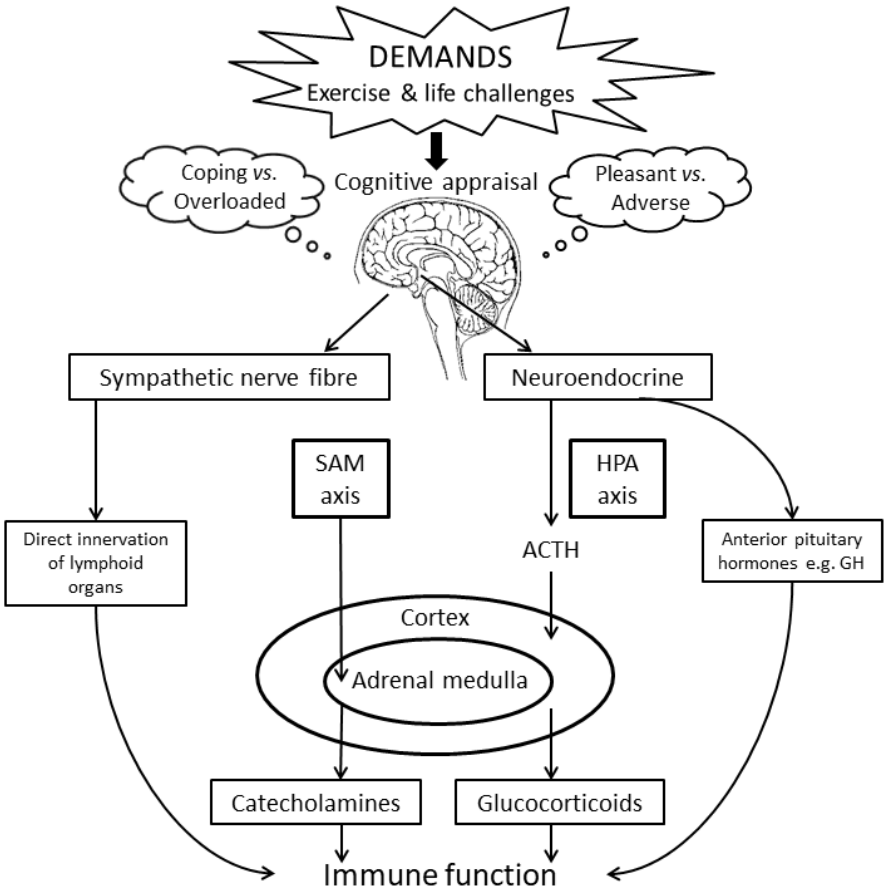

Heavy exercise
Nutritional deficits
Life stress
Lowered Immunity
Long-haul travel
Sleep disruption
Environmental extremes

Figure 2.


DEMANDS
Exercise & life challenges
Coping vs. Overloaded
Cognitive appraisal
Pleasant vs. Adverse
Sympathetic nerve fibre
Neuroendocrine
SAM axis
HPA axis
Direct innervation of lymphoid organs
ACTH
Anterior pituitary hormones e.g. GH
Cortex
Adrenal medulla
Catecholamines
Glucocorticoids
Immune function